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Abstract: OBJECTIVE: We investigated the effect of alcohol on the cervical and ocular vestibular evoked myogenic potentials (cVEMPs and oVEMPs). As alcohol produces gaze-evoked nystagmus (GEN), we also tested the effect of nystagmus independent of alcohol by recording oVEMPs during optokinetic stimulation (OKS). METHODS: The effect of alcohol was tested in 14 subjects over multiple rounds of alcohol consumption up to a maximum breath alcohol concentration (BrAC) of 1.5‰ (mean 0.97‰). The effect of OKS was tested in 11 subjects at 5, 10 and 15deg/sec. RESULTS: oVEMP amplitude decreased from baseline to the highest BrAC level by 27% (range 5-50%, P<0.001), but there was no significant effect on oVEMP latency or cVEMP amplitude or latency. There was a significant negative effect of OKS on oVEMP amplitude (16%, P=0.006). CONCLUSIONS: We found a selective effect of alcohol on oVEMP amplitude, but no effect on the cVEMP. Vertical nystagmus elicited by OKS reduced oVEMP amplitude. SIGNIFICANCE: Alcohol selectively affects oVEMP amplitude. Despite the effects of alcohol and nystagmus, both reflexes were reliably recorded in all subjects and conditions. An absent response in a patient affected by alcohol or nystagmus indicates a vestibular deficit.

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The effect of alcohol on cervical and ocular vestibular evoked myogenic potentials in healthy volunteers

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Highlights:

- Consumption of alcohol up to a maximum BrAC of 1.5 ‰ (mean 0.97 ‰) had a selective dampening effect on oVEMP amplitude, while there was no effect of alcohol on oVEMP latency or cVEMP amplitude or latency
- Optokinetic stimulation also reduced oVEMP amplitude by decreasing the mean level of gaze and inferior oblique muscle activity throughout the recording
- cVEMPs and oVEMPs can be reliably recorded in subjects who are under the influence of alcohol or have nystagmus, providing that they can cooperate and achieve a reasonable mean level of up-gaze during the recording

Abstract

Objective: We investigated the effect of alcohol on the cervical and ocular vestibular evoked myogenic potentials (cVEMPs and oVEMPs). As alcohol produces gaze-evoked nystagmus (GEN), we also tested the effect of nystagmus independent of alcohol by recording oVEMPs during optokinetic stimulation (OKS).
Methods: The effect of alcohol was tested in 14 subjects over multiple rounds of alcohol consumption up to a maximum breath alcohol concentration (BrAC) of 1.5‰ (mean 0.97‰). The effect of OKS was tested in 11 subjects at 5, 10 and 15 deg/sec.
Results: oVEMP amplitude decreased from baseline to the highest BrAC level by 27% (range 5-50%, $P < 0.001$), but there was no significant effect on oVEMP latency or cVEMP amplitude or latency. There was a significant negative effect of OKS on oVEMP amplitude (16%, $P = 0.006$).
Conclusions: We found a selective effect of alcohol on oVEMP amplitude, but no effect on the cVEMP. Vertical nystagmus elicited by OKS reduced oVEMP amplitude.
Significance: Alcohol selectively affects oVEMP amplitude. Despite the effects of alcohol and nystagmus, both reflexes were reliably recorded in all subjects and conditions. An absent response in a patient affected by alcohol or nystagmus indicates a vestibular deficit.

Introduction

Alcohol has been shown to have significant and widespread effects on the central nervous system. As acute alcohol intoxication commonly produces vertigo and imbalance, the effect of alcohol on vestibular function has been the focus of many studies. For example, research has demonstrated impairment of standing balance in healthy human volunteers after consumption of alcohol (e.g. Kubo et al., 1989; Modig et al., 2012a,b; Savolainen et al., 1980). The greatest deficits typically occur on tasks thought to rely on vestibular input, i.e. in which visual and proprioceptive cues are absent or misleading, such as standing with eyes closed on an unstable surface (Goebel et al., 1995; Ledin and Ödqvist, 1991; Tianwu et al., 1995; Woollacott, 1983). The clearest evidence of a direct effect of alcohol on the peripheral vestibular organs is the occurrence of positional alcohol nystagmus (PAN), in which alcohol is thought to change the specific gravity of the cupula, causing the semicircular canals to become sensitive to gravity and evoking nystagmus when the head is tilted laterally (Aschan and Bergstedt, 1975; Fetter et al., 1999).

To investigate whether alcohol affects the detection or transmission of vestibular sensory information, studies have measured its effect on vestibular reflexes, predominantly the vestibulo-ocular reflex (VOR). Alcohol has been shown to significantly diminish the nystagmus evoked by both caloric irrigation and horizontal angular rotation (Berthoz et al., 1977; Bochenek and Ormerod, 1962; Chiang and Young, 2007; Post et al., 1994; Tianwu et al., 1995). Similarly, alcohol decreases dynamic visual acuity during vertical translations, though the gain of the translational VOR does not appear to be affected (Schmäl et al., 2000, 2003). Studies of ocular counterrolling have shown a small decrease in torsion after alcohol consumption (Diamond and Markham, 2008; Markham and Diamond, 2006). In contrast, there does not appear to be an effect of alcohol on the perception of subjective visual vertical (SVV) either during standard test administration (Zingler et al., 2003) or during eccentric

rotation (Lindgren et al., 1998), though there tends to be an alcohol-related increase in visual field dependence on the rod and frame test (Hafstrom et al., 2007).

While these studies point to significant effects of alcohol on the vestibular system, it is not clear whether the effects occur in the peripheral vestibular organs or along central vestibular pathways, such as in the brainstem or cerebellum. Alcohol has well-documented, detrimental effects on the central systems involved in vestibular and oculomotor function. With higher doses of alcohol saccades have slower velocity and longer latency, while smooth pursuit has decreased gain and becomes increasingly saccadic (Baloh et al., 1979; Barnes, 1984; Bittencourt et al., 1980; Fransson et al., 2010; Holdstock and de Wit, 1999; Wilkinson et al., 1974). The gain and slow phase velocity of optokinetic nystagmus also tends to be decreased with alcohol (Baloh et al., 1979; Tianwu et al., 1995) and the ability to suppress the VOR during head motion is diminished (Barnes, 1984; Harder and Reker, 1995). One of the best-documented oculomotor effects of alcohol consumption is gaze-evoked nystagmus (GEN), resulting from a deficit in gaze-holding and the neural integrator (e.g. Booker, 2001; Goding and Dobie, 1986).

It is also not clear whether there is a difference in the sensitivity of the semicircular canals or otolith organs to alcohol. On tests specific to the otoliths, such as ocular counterrolling, SVV and the translational VOR, alcohol effects have typically been small or non-significant. We therefore wished to investigate the effect of alcohol on two otolith-dependent vestibular reflexes, the cervical and ocular vestibular evoked myogenic potentials (cVEMPs and oVEMPs). VEMPs are short-latency muscle reflexes recorded from the neck and extraocular muscles in response to vestibular stimulation with brief bursts of sound or vibration (see Rosengren et al., 2010 for review). The cVEMP is recorded with surface electrodes from the sternocleidomastoid (SCM) muscle ipsilateral to the stimulated ear and consists of a biphasic positive-negative waveform with peak latencies at approximately 13 and 23 ms (i.e. p13-n23). In contrast, the oVEMP is recorded predominantly from the inferior

oblique extraocular muscle contralateral to the stimulated ear from electrodes placed beneath the eyes. It consists of a biphasic negative-positive peak with latencies of approx. 10 and 15 ms (n10-p15). Recordings from single motor units in these muscles have shown that the cVEMP is produced by a short-latency inhibition of the SCM and the oVEMP by an excitation of the inferior oblique muscle (Colebatch and Rothwell, 2004; Weber et al., 2012). As sound and vibration have been shown to preferentially activate the otoliths, with the semicircular canals activated to a lesser extent (Curthoys et al., 2006; Murofushi and Curthoys, 1997; Zhu et al., 2011), VEMPs are thought to reflect the integrity of the otolith organs. The particular otolith organ responsible for each type of VEMP evoked by different stimuli is still controversial (e.g. Papathanasiou, 2012). Studies in patients with differential dysfunction of one vestibular nerve bundle suggest that the air-conducted sound-evoked cVEMP is a test mainly of inferior vestibular nerve afferents (Rosengren and Kingma, 2013). Similar research suggests that the skull vibration-evoked oVEMP is a test mainly of superior nerve afferents (Rosengren and Kingma, 2013), but this might depend upon the particular vibration stimulus used. Combined, this evidence suggests that the sound-cVEMP might originate predominantly in the saccule and, depending on the stimulus, the vibration-oVEMP mainly in the utricle. The reflexes also test two different pathways: the vestibulo-collic (VCR) and vestibulo-ocular (VOR) reflex pathways. We tested the effect of alcohol on cVEMPs evoked by air-conducted sound and oVEMPs evoked by skull vibration. We chose these stimuli as they produce the most robust responses for each reflex. Only one study has previously investigated the effect of alcohol on the cVEMP (Chiang and Young, 2007). The authors tested normal volunteers before and after consumption of a dose of alcohol designed to bring subjects close to the local legal limit for driving. They found no effect of alcohol on sound-evoked cVEMP amplitude, but a small elongation of p13 latency. To extend these findings, we aimed to measure both cVEMPs and oVEMPs at multiple breath alcohol concentration (BrAC) levels up to a higher maximum of 1.5 ‰ (per mil).

As alcohol is known to produce GEN, we also considered whether the presence of nystagmus per se might affect oVEMPs independent of the effect of alcohol. oVEMPs are also very sensitive to the angle of vertical gaze: they are typically recorded from beneath the eyes with gaze directed upwards (Govender et al., 2009). The n10 oVEMP peak is largest in this position because it originates in the inferior oblique muscle, which is active and close to the recording electrodes during up-gaze (Rosengren et al., 2013; Weber et al., 2012). With increasing alcohol consumption the incidence and strength of GEN increase, changing the average direction of gaze and possibly altering oVEMP amplitude. We sought to mimic the effect of GEN in sober volunteers by recording oVEMPs during optokinetic stimulation (OKS).

Methods

Participants

Fourteen healthy volunteers participated in Experiment 1: the effect of alcohol on cVEMPs and oVEMPs (mean age 29 years, range 24-38 years; 10 males, 4 females). Eleven different volunteers participated in Experiment 2: the effect of OKS on oVEMPs (mean age 33 years, range 26-46 years; 4 males, 7 females). In both cases the participants had no history of vestibular dysfunction, neurological disease or alcohol dependence. The participants gave informed written consent according to the Declaration of Helsinki and the study was approved by the local ethics committee (Kantonale Ethik-Kommission Zurich, 2010-0468).

Measurements

cVEMP recording

The cVEMP stimulus was an unshaped burst of sound (500 Hz, 4 ms), delivered at 126 dB peak SPL using headphones and a custom amplifier (TDH 39, Telephonics Corp.). The stimuli were generated with customized software using a laboratory interface

(micro1401, Cambridge Electronic Design (CED)) and delivered at a rate of 7.5 Hz for 200 repetitions per trial. Subjects reclined to ~30 deg above horizontal and lifted and turned their heads away from the side of the stimulus for the duration of each trial. SCM muscle activity was recorded from surface electrodes (Blue sensor N, Ambu A/S) placed over the SCM muscle belly (active) and medial clavicle (reference). An earth electrode was placed on the sternum, and all electrodes remained in place between rounds. EMG was sampled at 10 kHz from 20 ms before to 80 ms after stimulus onset, amplified and bandpass filtered (5 Hz to 2 kHz), using the same micro1401 data acquisition interface and custom software as described above. Negative potentials at the active electrodes were displayed as upward deflections. cVEMPs were recorded using unrectified EMG, while the strength of background SCM muscle contraction was monitored and recorded using rectified EMG to allow approximate matching of contraction levels across trials. Amplitudes and latencies were measured at the p13 and n23 response peaks. Peak-to-peak amplitude was expressed as the ratio of raw peak-to-peak amplitude to the mean rectified EMG measured over the 20 ms baseline period. To reduce the effect of inter-trial variability, two trials were recorded for each side during each experimental condition and the amplitudes and latencies averaged.

oVEMP recording

oVEMPs were elicited by bursts of skull vibration (500 Hz, 4 ms) delivered with a hand-held 'minishaker' positioned over the hairline (delivered at ~148 dB force level (FL) peak; minishaker model 4810, amplifier model 2706, Brüel & Kjaer P/L). The minishaker was applied near Fz, based on the international 10-20 electrode placement convention (Rosengren et al., 2013). This stimulus produces predominantly interaural head acceleration with an initial peak amplitude of ~0.1 *g* and initial peak frequency of around 350 Hz in the interaural axis (Weber et al., 2012), while contributions of rotation cannot be ruled out. The acceleration measured at the mastoid was lower than the stimulus drive of 500 Hz due to the

sharp onset of the stimulus and the impulse response of the skull. A sample accelerometry trace from a single subject is shown in Figure 1. The vibration oVEMP evoked by this stimulus is likely to be mediated by fibres in the superior vestibular nerve as the mastoid acceleration is predominantly interaural, potentially activating utricular fibres, and the stimulus is similar to that found to produce oVEMPs dependent upon superior nerve fibres.

A total of 200 repetitions per trial were delivered at a rate of 7.5 Hz. A guide mark was drawn at Fz to facilitate reproducible placement of the minishaker between trials. Subjects reclined as described above and directed their gaze upwards to a fixed point on the ceiling. The angle of the bed was similar in the two oVEMP experiments. Surface potentials were recorded with an active electrode placed over the infra-orbital margin and a reference directly below it on the cheek. An earth electrode was placed on the sternum, and all electrodes remained in place between rounds. Data were sampled at 10 kHz from 10 ms before to 60 ms following stimulus onset using the same filter settings and equipment as described above. Amplitudes and latencies were measured at the n10 and p15 response peaks and amplitude was expressed as peak-to-peak value. As for the cVEMP, two trials were recorded in each experimental condition and the amplitudes and latencies averaged.

Breath alcohol measurement

Breath alcohol concentration was measured with the Dräger Alcotest 6510 (Drägerwerk AG & Co. KgaA, Lübeck, Germany), which is approved by the Swiss Federal Roads Office (FEDRO) for BrAC testing and is accurate to within 5%. Subjects were instructed to inspire deeply and then expire slowly into the detector until signalled to stop. To ensure sufficient effects of alcohol, subjects were tested at least 30 minutes after their first sip of alcohol. To prevent erroneous high BrAC readings, they were tested at least 5 minutes after their last sip of alcohol and following a sip of non-alcoholic drink and/or food (see Experimental Procedure and Figure 2 for details). The BrAC measurement was taken both

immediately before and immediately after VEMP testing (in all except the first session, when measurements were taken only before VEMP testing) and the results averaged to account for any changes in BrAC level over the course of each 10 min test round.

Optokinetic stimulation

To record oVEMPs during optokinetic stimulation, subjects reclined to approximately 30 deg from horizontal on a bed in front of the lower edge of a translucent screen (1.6 x 0.9 m) tilted to the same angle. In the baseline condition, subjects were asked to look upwards toward a target at the centre of the screen (rear projection from Panasonic HD beamer PT-AE3000E). The vertical gaze angle in this position was 30 deg and target distance was 104 cm. Optokinetic stimulation consisted of 8 cm yellow and blue bands travelling down the screen for a period of 1 min at velocities of 5, 10 and 15 deg/sec. During stimulation, subjects were asked to direct their gaze toward the centre of the screen without suppressing any nystagmus. No target was displayed during OKS as this may have suppressed nystagmus.

Optokinetic nystagmus (OKN) was recorded using a commercial video eye movement recording system (VO425, Interacoustics, Denmark) in all subjects. We were not able to record eye movements simultaneous to the oVEMP recordings due to restriction of vertical gaze by the goggles. The measurements were therefore made separately with a neutral (straight ahead) gaze angle at a distance of 100 cm from the centre of the screen. Eye velocity was measured automatically by the commercial software over each slow phase of nystagmus and measurement points were adjusted individually when necessary. Eye position was measured using the exported raw data. To estimate the magnitude of eye movements during OKS we calculated the standard deviation of eye position in degrees for each recording. Visual inspection of the data confirmed that this value provided a good measure of slow phase amplitude in subjects and was not unduly affected by occasional blinks. Both velocity and position were measured over the entire 1 min trial.

Experimental procedure

Experiment 1: The effect of alcohol on cVEMPs and oVEMPs

The subjects were tested in groups of three to five over four evening sessions (Figure 2). They consumed no food or beverages other than water during the six hours prior to the test. Subjects first underwent a baseline, pre-alcohol test recording of BrAC, cVEMPs and oVEMPs. The test order was: an initial BrAC measurement, 4 cVEMP recordings (each ear was stimulated twice) and 2 oVEMP recordings (midline forehead stimulation activated both ears simultaneously) and a second BrAC measurement. In half of the subjects oVEMPs were tested first and in the other half cVEMPs were tested first. Following the baseline test, each subject consumed their first dose of alcohol. The testing was repeated after the first round of consumption. Subjects then consumed their next dose. This procedure was repeated for each subject until either four rounds of alcohol consumption had been completed, the subject chose to end their participation or the maximum BrAC of 1.5 ‰ was reached. As shown in Figure 2, the subjects were tested in a staggered fashion as only one subject could be tested at once. Each test block (BrAC, cVEMP, oVEMP, BrAC) took approx. 10 minutes to complete and the duration of each round was approx. 45 mins for each subject. Snacks were typically provided for each subject after their first round of consumption was complete.

The standard dose of alcohol was 20 g (grams). In the first experimental session (3 subjects), subjects consumed one standard dose of wine (14.5% alcohol by volume [ABV]) during each round of alcohol consumption (i.e. 175 ml of wine each round). To increase the level of intoxication, in the three following experimental sessions, the remaining 11 subjects were given a choice of several different spirits: gin (37.5% alcohol by volume [ABV]), vodka, whisky or rum (all 40% ABV), mixed with either soft drink or juice to taste. For the 40% spirits this was equivalent to 63 ml of liquid and for the 37.5% spirit 68 ml. In these sessions,

subjects were asked to drink a double dose of 40 g in the first round of consumption, and a single dose of 20 g each round thereafter (as shown in Figure 2).

Experiment 2: The effect of optokinetic stimulation on oVEMPs

Baseline oVEMP recordings without OKS were performed at the beginning and end of each session. After the first baseline trial, oVEMPs were recorded during each of the three OKS velocities. The order of OKS trials was counterbalanced and the sequence was repeated to produce two trials at each stimulus velocity. The eye movement recordings were performed either directly before or after the oVEMP recordings in the same session. The order of OKN measurement trials was also counterbalanced.

Data analysis

There were no left-right differences and therefore data from the right and left ears were averaged. *Experiment 1*: We tested the change in BrAC over rounds of consumption with repeated measures ANOVA. To test the effect of alcohol on the reflexes, the data were analysed using a mixed model for each of the outcome variables using BrAC as a factor. Estimates and 95% confidence intervals for BrAC are presented for the outcome variables oVEMP amplitude, n10 latency, cVEMP amplitude and p13 latency. *Experiment 2*: We compared oVEMP amplitudes and latencies across OKS conditions using repeated measures ANOVA, ANCOVA and t-tests. We correlated slow phase eye velocity and slow phase amplitude with oVEMP amplitude using Pearson's correlations. In both experiments, normality was confirmed with Q-Q plots before analysis.

Results

Experiment 1: The effect of alcohol on cVEMPs and oVEMPs

At baseline BrAC was 0 ‰ for all subjects. Eight of the 14 subjects completed 4 rounds of alcohol consumption, while 6 stopped early. Two of these subjects reached the maximum BrAC of 1.5 ‰ at one of the rounds and stopped alcohol consumption at that point, while the other 4 subjects stopped after they reached their preferred limit (2 stopped in order to limit their levels of intoxication and 2 for reasons unrelated to their perceived level of intoxication). The BrAC levels across rounds are shown in Figure 3. With increasing alcohol consumption there was a significant increase in BrAC ($F_{(4,28)} = 48.2$, $P < 0.001$). At the last measurement point for each subject the mean BrAC was 0.97 ‰ (range 0.18 to 1.4 ‰, averaged over 2 measurements before and after VEMP testing). Female subjects had higher maximum BrAC values than males (1.14 vs 0.89 ‰), but the difference was not significant and, as there are no gender differences in sound- and vibration-evoked VEMPs, this did not affect the results.

The cVEMPs and oVEMPs recorded at baseline were present in all subjects except one, whose cVEMP was not reproducible and close to threshold. In this subject only oVEMPs were analysed. In one subject a technical fault prevented cVEMPs from being recorded during round 2. The means and standard deviations for reflex amplitudes and latencies at the baseline and last measurements are shown in Table 1, while the changes in BrAC and reflex amplitude and latency by round of alcohol consumption are shown in Table 2. There were no significant left-right differences and therefore data from the right and left ears was averaged. There was a significant relationship between BrAC and oVEMP amplitude (Figure 4), whereby oVEMP amplitude decreased with increasing BrAC ($\beta = -2.983$, $P < 0.001$). The mean overall decrease in oVEMP amplitude from baseline to the highest BrAC level measured was 27% and the range was 5 to 50 %. These values corresponded to a mean decrease in oVEMP amplitude of 3.3 μV (range 0.25 to 11.5 μV, effect size $d = 0.75$). The effect might have been greater if all subjects had participated in all

rounds of testing, as some of the subjects who stopped drinking early were those most sensitive to its effects.

There was a trend toward an increase in oVEMP latency with increasing alcohol consumption ($\beta = 0.056$, $P = 0.0634$), although the mean overall increase in latency between the baseline recording and highest BrAC level was only 0.04 ms (equivalent to 0.5 %; values ranged from a latency shortened by 1.9 % [0.18 ms] to a latency prolonged by 3.8 % [0.3 ms]). There was no significant relationship between BrAC and cVEMP amplitude or latency. Example traces from a single subject are shown in Figure 5.

Although gaze-evoked nystagmus was not measured in this experiment, we observed the presence of nystagmus during testing in most subjects. Four subjects in particular were noted to have very robust, up-beating gaze-evoked nystagmus by the last round of testing, and these are indicated (with an asterisk *) in Figures 3 and 4. In these subjects, there was no clear relationship between the presence of strong gaze-evoked nystagmus and the effect of alcohol on oVEMP amplitude.

Experiment 2: The effect of optokinetic stimulation on oVEMPs

oVEMPs were present in all subjects and conditions, and mean values are shown in Table 3. There was a significant detrimental effect of OKS on oVEMP amplitude (Figure 6A; $F_{(3,30)} = 8.1$, $P < 0.001$), though the effect was not related to the velocity of stimulation in a simple dose-dependent manner. Post hoc t-tests showed that the effect was due to significantly lower amplitude with stimulation at 10 deg/sec ($t_{(10)} = 4.1$, $P = 0.002$), while the other two velocities did not reach significance after correction for multiple comparisons ($t_{(10)} = 2.5$ and 2.9, $P = 0.032$ and 0.017, at 5 and 15 deg/sec respectively). Simple comparison of mean oVEMP amplitude with and without optokinetic stimulation demonstrated a significant negative effect of OKS on amplitude (i.e. averaged over the three stimulation velocities; $t_{(10)} = 3.5$, $P = 0.006$). The mean decrement in oVEMP amplitude during optokinetic stimulation

was 16% or 2.1 μV (d = 0.26). There was no effect of optokinetic stimulation on oVEMP latency at any velocity.

We wondered whether subjects whose oVEMPs decreased most during optokinetic stimulation were those who tended to have faster eye movements or larger OKN amplitudes. Although we were not able to measure eye movements simultaneously with oVEMPs, we measured the eye movement response to optokinetic stimulation in all subjects in the same session, albeit for technical reasons with gaze directed straight ahead instead of upwards as during the oVEMP recordings. Slow phase eye velocity differed between subjects (range 3.9 to 10.3 deg/sec averaged across conditions) and increased with increasing stimulation velocity (4.6 ± 1.2, 7.1 ± 2.1 and 8.5 ± 3.4 deg/sec at 5, 10 and 15 deg/sec, respectively ($F_{(2,20)} = 25.5$, $P < 0.001$). There were also large differences in the estimated size of slow phase eye movements between subjects (range 0.98 to 3.63 deg), and there was a small but significant increase in the size of eye movements with increasing stimulation velocity (1.6, 2.0 and 2.1 deg at 5, 10 and 15 deg/sec, respectively; $F_{(2,20)} = 5.1$, $P = 0.016$). Subjects who responded to optokinetic stimulation with higher velocities of eye movement had significantly greater decrements in oVEMP amplitude (Figure 6B; averaged over all stimulation frequencies; $r = 0.70$, $P = 0.016$). This also tended to be true of subjects with larger OKN amplitudes ($r = 0.57$, $P = 0.07$), as the size and velocity of eye movements were correlated with each other ($r = 0.79$, $P = 0.004$). When either of these variables was entered as a covariate into the above ANOVA (testing oVEMP amplitude across optokinetic stimulation conditions), the effect of optokinetic stimulation on oVEMP amplitude was abolished, suggesting that the velocity and/or amplitude of OKN (or a different, related variable) accounted for the effect.

Discussion

We found a selective effect of alcohol on the size of the oVEMP, but no effect on the cVEMP or on the latency of either reflex. As the oVEMP is a type of vestibulo-ocular reflex,

the results could be due to a selective effect of alcohol on one or more parts of the VOR pathway. However, as we could not counterbalance the order of testing, a selective alcohol-related compliance or fatigue effect on gaze may also have contributed to the results. Alternately, the effect of alcohol on the oVEMP could be a consequence of the changes in eye position produced by alcohol-induced gaze-evoked nystagmus (GEN). In GEN, a failure of gaze-holding means that gaze cannot be held at the periphery and the eyes drift back towards the neutral position, requiring repeated saccades to redirect the eyes toward the peripheral target (Leigh and Zee, 2006). In addition to affecting brainstem oculomotor pathways, GEN interferes with maintenance of an appropriate angle of gaze elevation during an oVEMP recording. Instead the mean gaze angle achieved over the recording period should be related to the size of the drift before each saccade is initiated (i.e. the mean amplitude and/or velocity of the slow phase of nystagmus). Gaze affects oVEMP amplitude by changing the activity of the inferior oblique muscle and possibly also by altering central VOR processes (Rosengren et al., 2013; Todd et al., 2012). We sought to investigate the effect of nystagmus without alcohol intoxication by recording oVEMPs during vertical optokinetic stimulation. Although OKS does not entirely replicate the processes involved in GEN, as these eye movements are produced by separate neural circuits under different gaze and stimulation conditions, it produces nystagmus in the same direction in normal sober subjects. We found a significant detrimental effect of OKS on oVEMP amplitude, which was not related to the stimulus velocity per se, but rather to the size and velocity of the evoked OKN slow phases. That is, subjects who tended to respond to all stimulus velocities with large/fast slow phases showed the greatest decrement in oVEMP amplitude to optokinetic stimulation (Figure 6B). In subjects with large/fast slow phases, the mean level of gaze was likely lower, leading to smaller oVEMPs. This relationship was strong, despite the fact that we were not able to record the eye movements and oVEMPs simultaneously with the same gaze angle. It was also not possible to compare the strength of nystagmus across the two experiments. Optokinetic

stimulation produced robust nystagmus in all subjects. In contrast, only a small degree of GEN was present in most subjects following alcohol consumption, but strong GEN was seen in only four subjects, and in these subjects the effects of alcohol on oVEMP amplitude were mixed. Thus GEN did not have a clear effect on the results, however a contribution of GEN cannot be ruled out. Instead, our data suggest that there may be a genuine effect of alcohol on the VOR as measured by the oVEMP reflex.

Where could an effect of alcohol occur?

As the oVEMP is produced by a signal that is transduced at the peripheral otolith organ, conducted through central vestibular pathways, and expressed as a change in muscle activity, an effect of alcohol could theoretically result from dysfunction at any part of the reflex. At the periphery, VEMPs are thought to be mediated predominantly by the striolar hair cells of the otoliths, though the exact origin of each type of VEMP under different stimulation and recording conditions is currently not unequivocally established (see Rosengren and Kingma, 2013, for review). There is evidence that sound-cVEMPs originates predominantly in the saccule and some vibration-oVEMPs mainly in the utricle. Therefore a selective effect of alcohol on oVEMP amplitude could theoretically indicate a predominant effect of alcohol on the utricle. Though there is no obvious reason for this to be the case, it might be possible given that there are significant anatomical differences between the otoliths; including the size, location, type of attachment to the temporal bone and orientation of hair cells with respect to the striola (Lindeman, 1973; Rosenhall, 1972; Uzun-Coruhlu et al., 2007). Markham and Diamond (2006) reported a decrease in ocular counterrolling after alcohol consumption, suggesting reduced sensitivity of the utricle to dynamic tilt. In contrast, a possible effect of alcohol on the sacculo-ocular reflex might be suggested by the finding that dynamic visual acuity was reduced during vertical translations after alcohol consumption (Schmäl et al., 2000, 2003). However in both cases the effects were thought to be caused by

changes in central VOR pathways and not by a direct effect of alcohol on the otolith organs. In addition, we used different modes of stimulation to evoke the reflexes (air-conducted sound for the cVEMP and bone-conducted vibration for the oVEMP) to best reflect current common clinical practice and because these modes produce the most robust reflexes. Therefore, though we consider it unlikely, a differential effect of alcohol on the mode of stimulus delivery (sound versus vibration) cannot be ruled out.

As the cVEMP is a type of VCR and the oVEMP a manifestation of the VOR, the selective effect of alcohol on the oVEMP might be related to differences in the motor systems or central vestibular pathways tested by the two reflexes. It is possible that excitatory (oVEMP) and inhibitory (cVEMP) reflexes respond differently to alcohol, or that the different properties of extraocular and neck muscles may underlie the differential sensitivity of the reflexes. Alternately, a centrally-mediated effect of alcohol on the VOR is well-accepted and is the most likely candidate for the effects seen here (e.g. Baloh et al., 1979). VOR gain is known to be affected by factors such as visual context, cognitive set and alertness (e.g. Ramat et al., 2005; Snyder and King, 1992). Animal studies show that alcohol can inhibit spike generation in the vestibular nucleus without causing conduction delay (e.g. Ikeda et al., 1980). It is possible that the change in oVEMP gain results from altered brainstem and/or cerebellar activity, although such early modulation of a short-latency VOR projection would be unusual. Brainstem lesions can abolish or cause latency prolongation of both types of VEMP, depending on the location, severity and type of lesion. Stroke usually leads to absent reflexes while multiple sclerosis typically causes latency prolongation (Itoh et al., 2001; Shimizu et al., 2000). In contrast, subtle effects on VEMP amplitude are normally difficult to detect due to the wide natural variation in VEMP amplitudes between and within subjects. We did not find significant latency prolongation for either reflex, suggesting that alcohol does not cause substantial conduction delay. A previous study of cVEMPs following a single, smaller dose of alcohol reported that cVEMP latency was prolonged by a mean of 0.5 ms (Chiang and

Young, 2007). Although we found a trend for oVEMP latency to be prolonged, the mean increase in latency was only 0.04 ms and the variability was large. Therefore the effect is unlikely to be clinically meaningful. Both of these values are much smaller than the typical delays of several milliseconds found in patients with multiple sclerosis, a disease known to slow conduction velocity (Sartucci and Logi, 2002).

Our results showing no effect of alcohol on cVEMP amplitude are consistent with those of Chiang and Young (2007) and suggest that either the VCR is less susceptible to alcohol or the cVEMP is not sufficiently sensitive. The lack of effect is unlikely to be due to insufficient dosage, as the BrAC levels reached in the current study were higher than those reported previously and reached a maximum of 1.5 ‰ with a mean highest BrAC of 0.97 ‰, well over the local legal limit for driving (0.5 ‰). The results are also not confounded by the Mellanby effect (wherein the effects of alcohol are greater during the ascending phase than the descending phase; Kalant, 1998) as the repeated dose design ensured that BrAC levels were rising at almost all measurement points (Figure 3). We minimized the impact of reflex variability by averaging over two trials and the right and left sides and were able to take into account tonic contraction of SCM to rule out a confounding effect of muscle fatigue on the cVEMP.

Clinical implications

Although alcohol had a detrimental effect on oVEMP amplitude overall, it is important to note that the reflexes were not frankly abnormal, there was no asymmetry and the effect only became obvious after averaging two trials for both sides. An intoxicated patient would most likely fall within the normal range on this test. In contrast to other oculomotor functions, such as saccades, VEMPs are therefore not suitable for use as markers of intoxication. In fact, the oVEMPs were surprisingly well-formed in both experiments, especially given the amount of nystagmus seen during OKS. The results of both experiments

have implications for the testing of patients with nystagmus. Vertical nystagmus will likely decrease the amplitude of oVEMPs, as the mean angle of gaze will be smaller than intended, however it should not abolish the response. Assuming that a patient is able to comply with the request to look upwards and achieves a reasonable mean level of up-gaze during the recording, an absent response should indicate a lesion along the VOR pathway, as usual. This is likely to be true of horizontal nystagmus as well, as horizontal gaze does not typically alter the oVEMP to the same degree as vertical gaze (Govender et al., 2009).

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Figure Legends

Figure 1. Example accelerometry traces from the right mastoid of a single subject. The largest initial acceleration occurred in the interaural y-axis, suggesting a bowing of the skull. The trace represents the average of 30 stimuli (500 Hz, 4 ms delivered near Fz).

Figure 2. The procedure for experiment 1: the effect of alcohol on cVEMPs and oVEMPs. The upper part of the figure shows a single round in detail, including the approximate time in minutes taken for each part. The order of VEMP tests was counterbalanced across subjects (shown by the arrow) and cVEMPs required more time as the ears were stimulated separately. Subjects were asked to stop drinking at least 5 minutes before the start of the next round, and did not necessarily use the whole 30 minutes to consume the drink. The lower part of the figure shows the procedure for a single recording session with 4 subjects. The crosses represent test blocks and the grey arrows show the consumption of alcohol. Testing was staggered as only 1 subject could be tested at a time. In most sessions (11 subjects), the first round of consumption consisted of two standard 20 g doses of alcohol (shown here), while in one session (3 subjects) a single standard dose was consumed during all rounds.

Figure 3. The change in breath alcohol concentration (BrAC) with successive rounds of alcohol consumption. With increasing consumption of alcohol, BrAC levels increased to a mean of 0.95 ‰. The four subjects who were noted to have robust gaze-evoked nystagmus are indicated with an asterisk (*).

Figure 4. Experiment 1: The effect of alcohol on oVEMP amplitude. oVEMP amplitude is expressed as a ratio compared to the baseline level. Alcohol significantly decreased oVEMP amplitude. The four subjects who were noted to have robust gaze-evoked nystagmus are indicated with an asterisk (*).

Figure 5. oVEMPs and cVEMPs recorded in subject 13 at different levels of alcohol intoxication. Part A. oVEMPs recorded at 4 levels of BrAC showed systematic decreases in amplitude with increasing intoxication. The grey bar represents vibration stimulus artefact. Part B. In this subject cVEMPs showed increased amplitude at some BrAC levels and decreased amplitude at others.

Figure 6. Part A. Experiment 2: The effect of optokinetic stimulation on oVEMP amplitude. oVEMP amplitude is expressed as a ratio compared to the baseline level. Data are shown for each subject and for the mean response (thick black line and dots). Optokinetic stimulation significantly decreased oVEMP amplitude. Part B. The relationship between oVEMP amplitude decrement and slow phase eye velocity during optokinetic stimulation. oVEMPs and nystagmus were recorded separately under different gaze conditions in the same subjects. Subjects who tended to have fast and large slow phases of nystagmus (averaged over the three stimulation velocities) were more likely to show a large decrease in oVEMP amplitude during optokinetic stimulation ($r = 0.70$). Note that the data in Experiments 1 (alcohol) and 2 (OKS) came from different subjects.

Table 1. The effect of alcohol on cVEMPs and oVEMPs

	Baseline		Last round				
	Mean	SD	Mean	SD	β	CI	P
cVEMP amplitude (ratio)	1.64	0.58	1.71	0.78	0.07	-0.096, 0.235	0.4008
cVEMP latency (ms)	14.64	1.6	14.70	1.3	0.038	-0.261, 0.337	0.8003
oVEMP amplitude (μV)	11.3	5.4	8.0	3.1	-2.983	-4.002, -1.963	<0.001
oVEMP latency (ms)	8.72	0.4	8.76	0.3	0.056	-0.003, 0.116	0.0634

Table 2. Effects of alcohol by round of alcohol consumption

		Baseline	Round 1	Round 2	Round 3	Round 4
BrAC[1]	Mean	0.00	0.56	0.73	0.91	1.03
	SD	0.00	0.34	0.36	0.31	0.32
	N	14	14	14	11	8
cVEMP Amplitude[2]	Mean	1	1.00	0.98	1.12	1.11
	SD	0	0.26	0.27	0.18	0.17
	N	13	13	12	10	7
cVEMP Latency	Mean	1	1.005	0.992	1.003	1.017
	SD	0	0.031	0.035	0.047	0.026
	N	13	13	12	10	7
oVEMP Amplitude	Mean	1	0.89	0.84	0.79	0.80
	SD	0	0.20	0.15	0.15	0.10
	N	14	14	14	11	8
oVEMP Latency	Mean	1	0.996	1.000	1.004	0.998
	SD	0	0.012	0.016	0.019	0.018
	N	14	14	14	11	8

[1]Raw BrAC values are shown in ‰. [2]For all other measures values are given as a ratio of the baseline.

Table 3. The effect of optokinetic stimulation on oVEMPs

		Baseline	5 deg/sec	10 deg/sec	15 deg/sec	P
oVEMP amplitude	Mean (μV)	12.6	11.2	9.8	10.5	<0.001
	SD	8.9	7.4	7.0	7.2	
oVEMP latency	Mean (ms)	9.4	9.4	9.3	9.3	0.472
	SD	1.0	1.0	0.9	0.9	

Figure 1

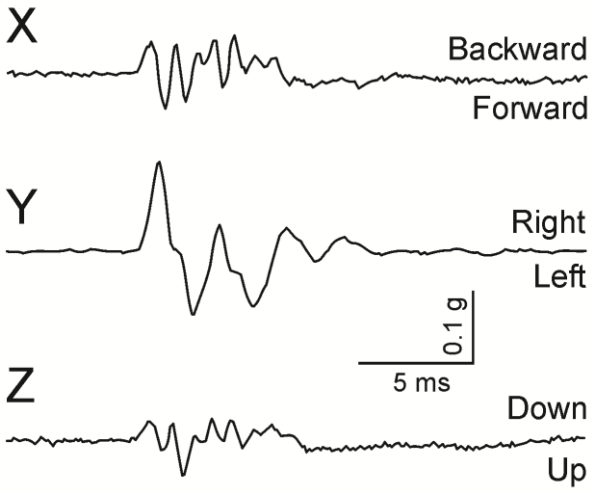


Figure 2

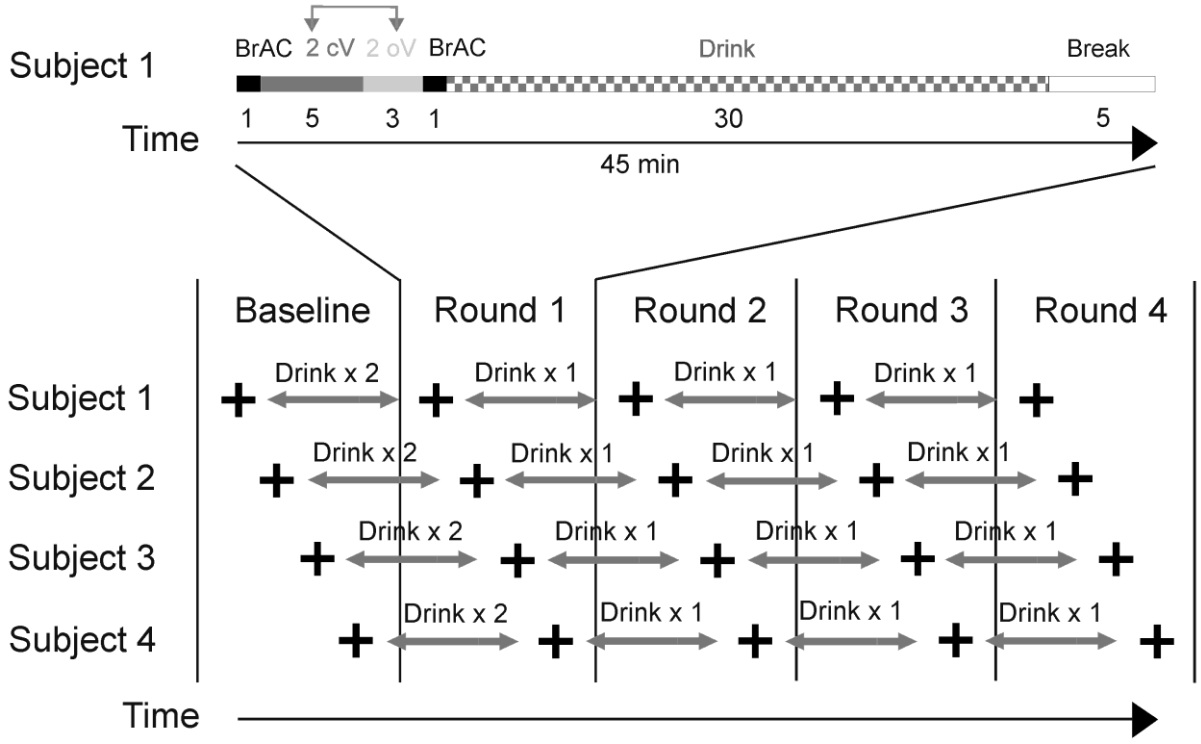

Subject 1
BrAC
2 cV
2 oV
BrAC
Drink
Break
1
5
3
1
30
5
Time
45 min
Baseline
Round 1
Round 2
Round 3
Round 4
Subject 1
Subject 2
Subject 3
Subject 4
Drink x 2
Drink x 1
Time

Figure 3

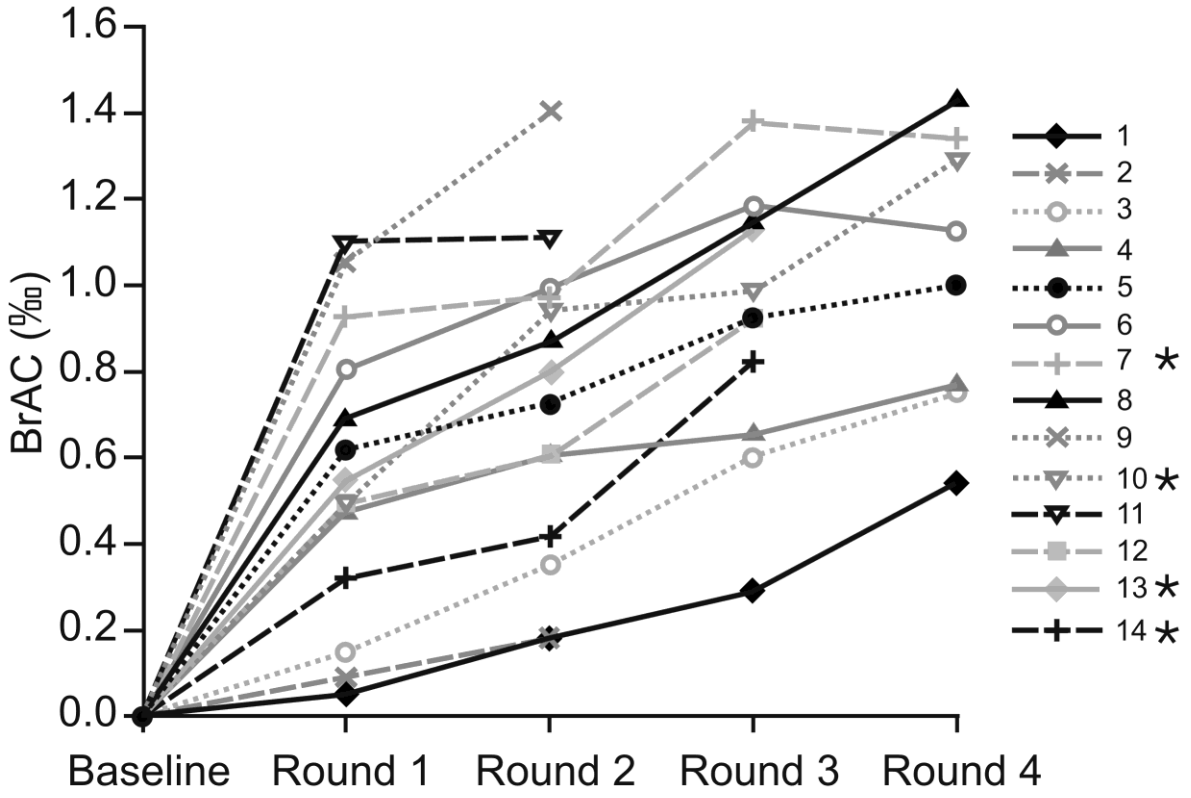

1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
BrAC (‰)
Baseline
Round 1
Round 2
Round 3
Round 4
1
2
3
4
5
6
7 *
8
9
10 *
11
12
13 *
14 *

Figure 4

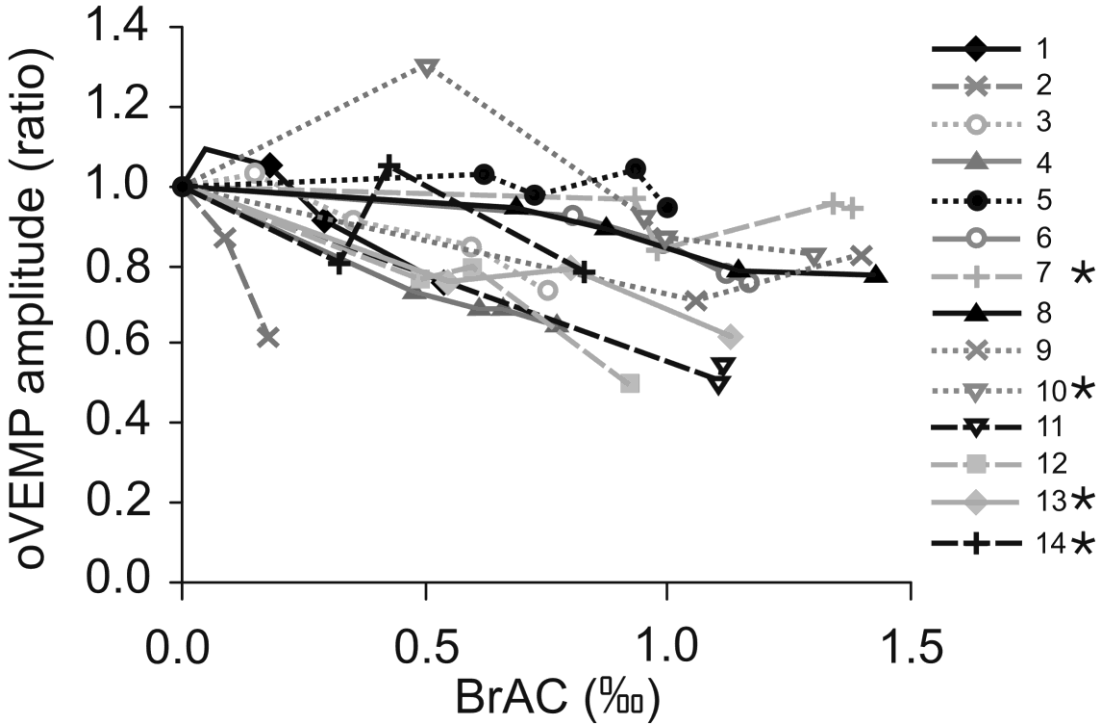

oVEMP amplitude (ratio)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.5
1.0
1.5
BrAC (‰)
1
2
3
4
5
6
7 *
8
9
10*
11
12
13*
14*

Figure 5

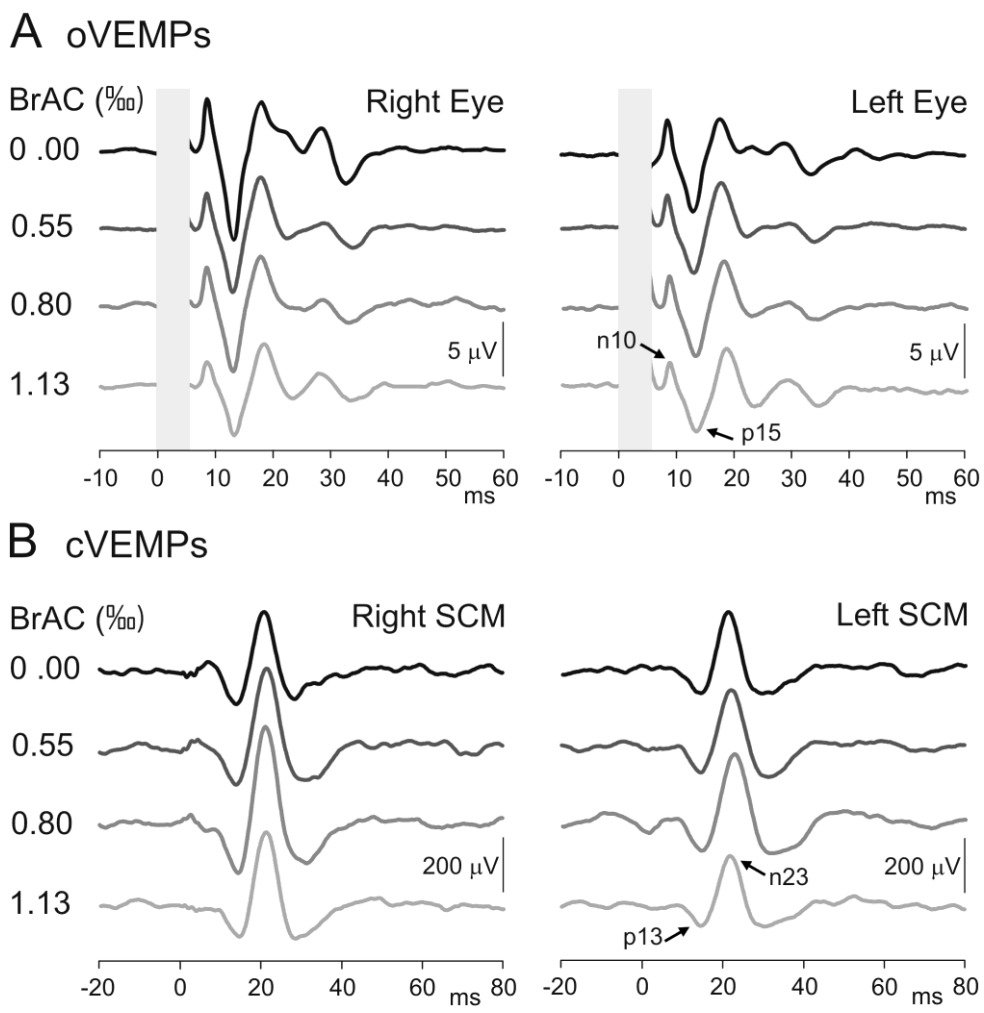
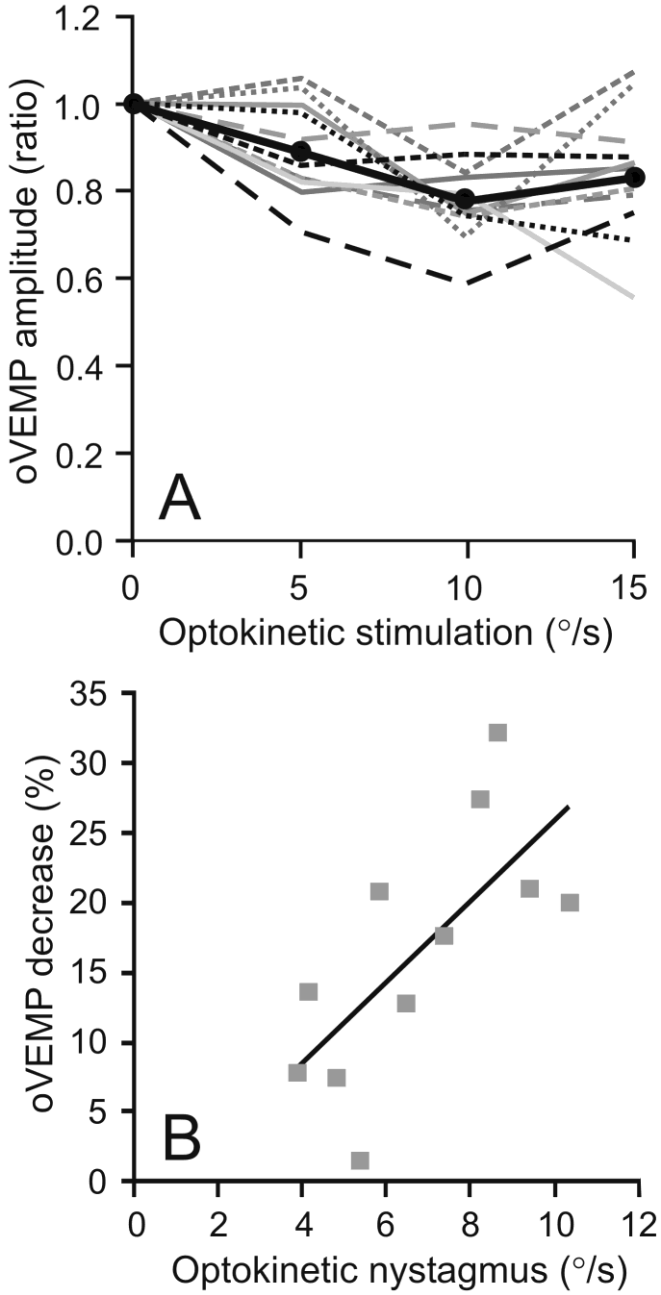

A oVEMPs
BrAC (‰)
Right Eye
Left Eye
0 .00
0.55
0.80
1.13
5 μV
n10
p15
-10 0 10 20 30 40 50 60
ms
B cVEMPs
Right SCM
Left SCM
200 μV
n23
p13
-20 0 20 40 60 80

Figure 6


1.2
1.0
0.8
0.6
0.4
0.2
0.0
oVEMP amplitude (ratio)
A
0
5
10
15
Optokinetic stimulation (°/s)
35
30
25
20
15
10
5
0
oVEMP decrease (%)
B
0
2
4
6
8
10
12
Optokinetic nystagmus (°/s)